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FILE 'USPAT' ENTERED AT 15:55:03 ON 05 OCT 1999

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  *         U. S.   P A T E N T   T E X T   F I L E                 *
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=> s cyclosporine

L1          707 CYCLOSPORINE

=> s e lung

       1482443 E
         20224 LUNG
L2           24 E LUNG
                (E(W)LUNG)

=> e lung

E#      FILE            FREQUENCY  TERM
--      ----            ---------  ----
E1      USPAT                   4     LUNEVA/BI
E2      USPAT                   1     LUNEX/BI
E3      USPAT               20224 --> LUNG/BI
E4      USPAT                   1     LUNG160:275-284/BI
E5      USPAT                   3     LUNGA/BI
E6      USPAT                   4     LUNGALLY/BI
E7      USPAT                   1     LUNGARELLA/BI
E8      USPAT                  13     LUNGAST01/BI
E9      USPAT                   1     LUNGBERG/BI
E10     USPAT                   1     LUNGBLAD/BI
E11     USPAT                   1     LUNGBURG/BI
E12     USPAT                   1     LUNGBUZZ/BI

=> s e3

L3        20224 LUNG/BI

=> s l1 and l3

L4          271 L1 AND L3

=> e aerosol

E#      FILE            FREQUENCY  TERM
--      ----            ---------  ----
E1      USPAT                   1     AEROSOIZED/BI
E2      USPAT                   1     AEROSOK/BI
E3      USPAT               28701 --> AEROSOL/BI
E4      USPAT                   1     AEROSOL0.01/BI
E5      USPAT                   1     AEROSOL501/BI
E6      USPAT                   1     AEROSOLA/BI
E7      USPAT                   3     AEROSOLABLE/BI
E8      USPAT                   1     AEROSOLADMINISTRATION/BI
E9      USPAT                   1     AEROSOLAEROGEL/BI
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E10 USPAT 1 AEROSOLATE/BI
E11 USPAT 4 AEROSOLATING/BI
E12 USPAT 5 AEROSOLATION/BI

=> s e3

L5 28701 AEROSOL/BI

=> s l1 and l5

L6 98 L1 AND L5

=> s l4 and l6

L7 51 L4 AND L6

=> d l7 1-51

1. 5,962,478, Oct. 5, 1999, Inhibition of tumor necrosis factor .alpha.; Solomon B. Margolin, 514/345, 311, 334 [IMAGE AVAILABLE]

2. 5,958,891, Sep. 28, 1999, Recombinant eukaryotic plasmids containing allergen-gene and use thereof for the prevention and/or treatment of allergic diseases; Ching-Hsiang Hsu, et al., 514/44; 435/320.1, 375 [IMAGE AVAILABLE]

3. 5,958,449, Sep. 28, 1999, Antibiotic formulation and use for bacterial infections; Evan M. Hersch, et al., 424/450; 264/4.3 [IMAGE AVAILABLE]

4. 5,939,528, Aug. 17, 1999, Crystalline FRAP complex; Jon C. Clardy, et al., 530/350; 536/23.1, 23.5 [IMAGE AVAILABLE]

5. 5,889,015, Mar. 30, 1999, Use of mometasone furoate for treating lower airway passage and **lung** diseases; Joel A. Sequeira, et al., 514/172, 826, 958 [IMAGE AVAILABLE]

6. 5,886,026, Mar. 23, 1999, Anti-angiogenic compositions and methods of use; William L. Hunter, et al., 514/449 [IMAGE AVAILABLE]

7. 5,863,787, Jan. 26, 1999, Kaposi's sarcoma-associated herpesvirus (KSHV) glycoprotein B (GB) and uses thereof; Yuan Chang, et al., 435/252.3, 6, 69.1, 69.3, 91.2, 91.4, 243, 252.1, 320.1, 325; 514/44; 530/350, 395; 536/23.72 [IMAGE AVAILABLE]

8. 5,861,500, Jan. 19, 1999, Kaposi's sarcoma-associated herpesvirus (KSHV) interleukin 6 (IL-6) and uses thereof; Yuan Chang, et al., 536/23.72; 424/147.1, 159.1, 192.1, 229.1; 435/6, 69.1, 69.3, 235.1, 252.1, 320.1, 325; 530/350, 388.3; 536/23.4, 24.3, 24.33, 24.5 [IMAGE AVAILABLE]

9. 5,858,999, Jan. 12, 1999, Cosolvent parenteral formulation of tirilazad; Ching-Chiang Su, et al., 514/176, 247, 249, 408 [IMAGE AVAILABLE]

10. 5,858,985, Jan. 12, 1999, Treatment of asthma with fructose-1,6-diphosphate; Angel K. Markov, 514/25, 23, 826; 536/117 [IMAGE AVAILABLE]

11. 5,858,974, Jan. 12, 1999, Anti-fungal peptides; Roger G. Little, II, et al., 514/12, 9, 11, 13, 14, 15, 16, 17; 530/317, 324, 327, 328, 329 [IMAGE AVAILABLE]

12. 5,854,418, Dec. 29, 1998, Kaposi's sarcoma-associated herpesvirus (KSHV) viral macrophage inflammatory protein-1.alpha. II (vMIP-1.alpha. II) and uses thereof; Yuan Chang, et al., 536/23.72; 424/147.1, 159.1, 192.1, 229.1; 435/6, 69.1, 69.3, 235.1, 252.1, 320.1, 325; 530/350, 388.3; 536/23.4, 24.3, 24.33, 24.5 [IMAGE AVAILABLE]

13. 5,854,398, Dec. 29, 1998, Kaposi's sarcoma-associated herpesvirus (KSHV) interleukin 6 (IL-6) and uses thereof; Yuan Chang, et al., 530/387.1; 424/141.1, 147.1, 159.1, 186.1, 229.1; 435/7.1, 69.3; 436/548; 530/388.1, 388.3, 389.1; 536/23.72 [IMAGE AVAILABLE]

14. 5,837,699, Nov. 17, 1998, Use of mometasone furoate for treating upper airway passage diseases; Joel A. Sequeira, et al., 514/169, 172, 176, 182 [IMAGE AVAILABLE]

15. 5,837,491, Nov. 17, 1998, Polynucleotides encoding gelonin sequences; Marc D. Better, et al., 435/69.1, 252.3, 320.1; 536/23.4, 23.53, 23.6 [IMAGE AVAILABLE]

16. 5,831,064, Nov. 3, 1998, Kaposi's sarcoma-associated herpes virus (KSHV) interferon consensus sequence binding protein (ICSBP) and uses thereof; Yuan Chang, et al., 536/23.72; 424/229.1; 435/235.1, 320.1; 530/350 [IMAGE AVAILABLE]

17. 5,830,759, Nov. 3, 1998, Unique associated Kaposi's sarcoma virus sequences and uses thereof; Yuan Chang, et al., 435/372.2, 235.1, 252.3, 320.1, 325; 536/23.72, 24.32 [IMAGE AVAILABLE]

18. 5,829,435, Nov. 3, 1998, Prefilter for prevention of clogging of a nozzle in the generation of an **aerosol** and prevention of administration of undesirable particles; Reid Rubsamen, et al., 128/203.21, 200.14, 203.23 [IMAGE AVAILABLE]

19. 5,801,042, Sep. 1, 1998, Unique associated Kaposi's sarcoma virus sequences and uses thereof; Yuan Chang, et al., 435/252.3, 320.1, 325; 536/23.72, 24.32 [IMAGE AVAILABLE]

20. 5,795,986, Aug. 18, 1998, Pyrimido[4,5-B]indoles; Gordon L. Bundy, et al., 544/115, 250 [IMAGE AVAILABLE]

21. 5,788,968, Aug. 4, 1998, Methods and compositions for suppressing allograft rejection in mammals; Howard L. Weiner, et al., 424/184.1, 185.1; 530/350 [IMAGE AVAILABLE]

22. 5,786,344, Jul. 28, 1998, Camptothecin drug combinations and methods with reduced side effects; Mark J. Ratain, et al., 514/100, 211 [IMAGE AVAILABLE]

23. 5,759,571, Jun. 2, 1998, Antibiotic formulation and use for drug resistant infections; Evan M. Hersch, et al., 424/450 [IMAGE AVAILABLE]

24. 5,756,699, May 26, 1998, Immunotoxins comprising ribosome-inactivating proteins; Marc D. Better, et al., 536/23.4; 435/69.4, 69.5, 69.7; 536/23.51, 23.52, 23.53, 23.6 [IMAGE AVAILABLE]

25. 5,756,121, May 26, 1998, Antibiotic formulation and use for drug resistant infections; Kevin R. Bracken, 424/450; 264/4.1, 4.3 [IMAGE AVAILABLE]

26. 5,756,120, May 26, 1998, Antibiotic formulation and use for drug resistant infections; Evan M. Hersch, et al., 424/450 [IMAGE AVAILABLE]

27. 5,744,580, Apr. 28, 1998, Immunotoxins comprising ribosome-inactivating proteins; Marc D. Better, et al., 530/377, 351, 370, 387.3, 391.1, 391.5, 391.7, 391.9, 399 [IMAGE AVAILABLE]

28. 5,716,981, Feb. 10, 1998, Anti-angiogenic compositions and methods of use; William L. Hunter, et al., 514/449; 128/898; 526/304; 528/421; 604/20, 21, 96, 269, 508; 606/198; 623/12 [IMAGE AVAILABLE]

29. 5,681,556, Oct. 28, 1997, Method and compositions for suppressing allograft rejection in mammals; Howard L. Weiner, et al., 424/85.1, 85.2; 514/8; 530/395 [IMAGE AVAILABLE]

30. 5,633,279, May 27, 1997, 5-substituted derivatives of mycophenolic acid; David Morgans, Jr., et al., 514/468, 232.8, 320, 432; 544/153; 546/196; 549/13, 299 [IMAGE AVAILABLE]

31. 5,627,153, May 6, 1997, Anti-fungal methods and materials; Roger G. Little, II, et al., 514/12, 21; 530/324, 350, 380 [IMAGE AVAILABLE]

32. 5,621,083, Apr. 15, 1997, Immunotoxins comprising ribosome-inactivating proteins; Marc D. Better, et al., 530/391.9, 326, 370, 387.3, 391.7; 536/23.53 [IMAGE AVAILABLE]

33. 5,616,490, Apr. 1, 1997, Ribozymes targeted to TNF-.alpha. RNA; Sean M. Sullivan, et al., 435/366, 6, 91.31, 320.1, 325, 364, 367; 536/23.1, 23.2, 24.5 [IMAGE AVAILABLE]

34. 5,554,612, Sep. 10, 1996, 4-amino 6-substitutes mycophenolic acid and derivatives; John W. Patterson, et al., 514/233.5, 470; 544/153; 546/196; 548/525; 549/13, 60, 307 [IMAGE AVAILABLE]

35. 5,538,969, Jul. 23, 1996, 4-amino derivatives of 5-substituted mycophenolic acid; David Morgans, Jr., et al., 514/233.5, 422, 444, 450, 459, 470; 544/153; 548/230, 525; 549/60, 310 [IMAGE AVAILABLE]

36. 5,536,747, Jul. 16, 1996, 6-substituted mycophenolic acid and derivatives; John W. Patterson, et al., 514/470 [IMAGE AVAILABLE]

37. 5,529,923, Jun. 25, 1996, Flavobacterium strain; Richard C. Honour, et al., 435/252.1, 850 [IMAGE AVAILABLE]

38. 5,525,602, Jun. 11, 1996, Method of using 4-amino 6-substituted mycophenolic acid and derivatives; John W. Patterson, et al., 514/233.5, 320, 422, 432, 444, 450, 459, 470; 549/307 [IMAGE AVAILABLE]

39. 5,512,568, Apr. 30, 1996, Method of using 4-amino derivatives of 5-substituted mycophenolic acid; David Morgans, Jr., et al., 514/233.5, 320, 422, 432, 444, 450, 459, 470; 549/310 [IMAGE AVAILABLE]

40. 5,493,030, Feb. 20, 1996, 5-substituted derivatives of mycophenolic acid; David Morgans, Jr., et al., 548/230; 549/310 [IMAGE AVAILABLE]

41. 5,444,072, Aug. 22, 1995, 6-substituted mycophenolic acid and derivatives; John W. Patterson, et al., 514/320, 432, 473; 546/196; 549/13, 305 [IMAGE AVAILABLE]

42. 5,441,953, Aug. 15, 1995, 4- amino derivatives of mycophenolic acid; Eric B. Sjogren, 514/233.5, 320, 365, 385, 403, 422; 544/153; 546/196; 548/146, 311.4, 364.4; 549/310 [IMAGE AVAILABLE]

43. 5,416,202, May 16, 1995, Materials comprising and methods of preparation and use for ribosome-inactivating proteins; Susan L. Bernhard, et al., 536/23.2; 435/252.33, 320.1 [IMAGE AVAILABLE]

44. 5,380,879, Jan. 10, 1995, Derivatives of mycophenolic acid; Eric B. Sjogren, 549/310; 544/153; 546/196; 548/146, 311.4, 364.4, 525 [IMAGE AVAILABLE]

45. 5,376,546, Dec. 27, 1994, Analogs of ribosome-inactivating proteins; Susan L. Bernhard, et al., 435/199; 530/350, 370 [IMAGE AVAILABLE]

46. 5,362,735, Nov. 8, 1994, Rapamycin derivatives; Juan I. Luengo, 514/291; 540/456 [IMAGE AVAILABLE]

47. 5,321,043, Jun. 14, 1994, Method of combatting transplant rejection; Lynette J. Dumble, 514/454, 569 [IMAGE AVAILABLE]

48. 5,248,499, Sep. 28, 1993, Control of microbial infections in transplant patients; Christine Czarniecki, et al., 424/85.2, 85.1, 85.5 [IMAGE AVAILABLE]

49. 5,190,972, Mar. 2, 1993, Method of combatting **cyclosporine** organ toxicity with prostaglandin analogs; Lynette J. Dumble, 514/454, 569 [IMAGE AVAILABLE]

50. 5,078,999, Jan. 7, 1992, Method of treating systemic lupus erythematosus; Linda M. Warner, et al., 424/122; 514/291 [IMAGE AVAILABLE]

51. 5,049,388, Sep. 17, 1991, Small particle **aerosol** liposome and liposome-drug combinations for medical use; Jack V. Knight, et al., 424/450; 264/4, 4.1; 424/43; 428/402.2 [IMAGE AVAILABLE]

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     (FILE 'USPAT' ENTERED AT 15:55:03 ON 05 OCT 1999)
L1           707 S CYCLOSPORINE
L2            24 S E LUNG
                 E LUNG
L3         20224 S E3
L4           271 S L1 AND L3
                 E AEROSOL
L5         28701 S E3
L6            98 S L1 AND L5
L7            51 S L4 AND L6
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US PAT NO: 5,049,388 [IMAGE AVAILABLE] L7: 51 of 51
TITLE: Small particle **aerosol** liposome and liposome-drug combinations for medical use

ABSTRACT:
Disclosed are aqueous **aerosol** droplets containing liposome or interacted liposome-drug or medication combination particles in a continuous phase of air or oxygen-enriched air advantageous. . . that on its rupture the drug or medication is not lost from the liposome. Different methods of preparation of the **aerosol** particles containing the liposome and interacted liposome-drug combination particles are described which can be used in small particle **aerosol** treatment. The majority of the **aerosol** droplets containing the liposome particles alone or with drugs has a diameter less than 5 microns and has an aerodynamic. . .

SUMMARY:

BSUM(2)

The field of the invention is small particle **aerosol** liposomes and liposome-drug combinations advantageous for medical use.

SUMMARY:

BSUM(4)

Small particle **aerosol** is defined as a colloid system in which the continuous phase is a gas, and the majority of particles are. . . tract in substantial percentages. For example, 1.5 micron particles will deposit 46 percent of the total inhaled dose in the **lung** and another 36 percent in nose and upper air passages. Such uniform deposition will permit treatment of lesions at any level of the respiratory tract (Gilbert, B. E., Wilson, S. Z., and Knight, V., 1986, Ribavirin **Aerosol** Treatment of Influenza Virus Infections. In: Options for the Control of Influenza. UCLA Symposium on Molecular and Cellular Biology. Alan. . .

SUMMARY:

BSUM(5)

Small particle **aerosol** treatment delivers a high dose of drug to the epithelium of the respiratory tract in amounts largely unachievable by other. . .

SUMMARY:

BSUM(10)

Applicants are unaware of any prior art disclosing, suggesting, or teaching small particle aqueous **aerosol** droplets containing liposomes and liposome-drug particles propelled by air or oxygen-enriched air for medical use or that the heterogeneous size. . . particles (<1 micron in diameter) without leakage of the drug upon destruction of the liposome membranes. The size of the **aerosol** particle is controlled by the operating characteristics of the **aerosol** generator or nebulizer without any loss in effectiveness thereof.

SUMMARY:

BSUM(22)

The Lancet, "Dry Artificial **Lung** Surfactant and its Effect on Very Premature Babies", C. J. Morley, A. D. Banham, N. Miller, J. A. Davis, 1981. . .

SUMMARY:

BSUM(30)

Chemical Abstracts, 105:197191d (1986) discloses **aerosol** pharmaceuticals containing liposomes of 30-1000 mm diameter in a gas fluorocarbon. No mention is made of the **aerosol** particle size.

SUMMARY:

BSUM(31)

European Patent Application 0084898, 8/3/83, makes general references to nebulized aqueous suspensions without any indication as to the size of the **aerosol** particles.

SUMMARY:

BSUM(32)

Chemical Abstracts 103:27287f (1985) and International Application Publication No. W086/01714 (1986) disclose **aerosol**-liposome compositions.

SUMMARY:

BSUM(34)

The present invention is directed to small particle aqueous **aerosol** droplets containing liposomes and interacted drug-liposome combinations propelled in air or oxygen-enriched air having advantageous properties for medical use. Small particle **aerosol**, as used herein, is a colloid system in which the continuous phase is air or oxygen-enriched air, and the majority of **aerosol** particles is less than 5 microns in diameter with an aerodynamic mass median diameter ranging from 1 to 3 microns.. . . 10 microns in diameter. Advantaqeously, the partiole size of the liposomes and the liposome-drug particles are substantially homoqenized by the **aerosol** nebulizer to sizes of less than one micron in diameter. Most particles are much less than 1 .mu.m in diameter and several may be included in the aqueous particles generated by the **aerosol** generator. These smaller liposome and liposome-drug particles retain their pharmacological activity.

SUMMARY:

BSUM(35)

Small particle **aerosol** treatment containing liposomes alone is advantageous since liposomes can closely mimic pulmonary surfactant and may repair defects in this system. . .

SUMMARY:

BSUM(36)

Aerodynamic . . . Diameter" or equivalent mean diameter (An Introduction to Experimental Aerobiology, Robert L. Dimmick, Ann B. Alsers, Wiley Interscience, p. 447; **Aerosol** Science, C. N. Davies, Academic Press, 1966, p. 306).

SUMMARY:

BSUM(37)

Small particle **aerosol** treatment with interacted drug liposome particles is advantageous in that, when the liposome permeability barrier is damaged, such as during. . .

SUMMARY:

BSUM(38)

The . . . to be given by liposome-drug combinations range widely as does the dosage. In general, the drugs in recommended dosages for non-**aerosol** liposome-drug combinations of the prior art can be used

for the small particle **aerosol** liposome-drug combinations without the disadvantages of the prior art liposome-drug combinations. The amount of the drug in the liposome-drug combination **aerosol** is controlled by the concentration of drug in the reservoir of the **aerosol** generator. Also, the amount of drug employed depends on the duration of treatment, drug used and the like. For example,. . .

SUMMARY:

BSUM(40)

Accordingly, it is an object of the present invention to provide small particle aqueous **aerosol** containing liposomes or liposome-drug particles propelled or carried by air or oxygen- C enriched air for medical use.

SUMMARY:

BSUM(41)

A further object of the present invention is the provision of a method of processing liposomes by an **aerosol** nebulizer propelled by air or oxygen-enriched air from heterogeneous sizes to substantially uniform small particle liposomes (<1 micron in diameter). . .

SUMMARY:

BSUM(42)

A . . . object of the present invention is the provision of a method of processing interacted drug liposome combination particles by an **aerosol** nebulizer from heterogeneous sizes to substantially uniform, small particles of liposome-drug combinations carried in small particle aqueous droplets without premature. . .

SUMMARY:

BSUM(44)

A . . . object of the present invention is the provision of treating a patient by delivering with air or oxygen-enriched air small **aerosol** particles containing interacted drug liposome particles to the epithelium of the respiratory tract.

DRAWING DESC:

DRWD(2)

FIGS. . . . nebulizer, FIG. 1 being model No. 1920, and FIG. 1A being model No. 1917, useful in generating aqueous small particle **aerosol** droplets containing liposomes and liposome-drug particles in air or oxygen-enriched air of the invention.

DRAWING DESC:

DRWD(3)

FIG. 2 is an enlargement of the liposomes in the **aerosol** reservoir at the start of operation of the **aerosol** generator.

DRAWING DESC:

DRWD(5)

FIG. 4 is a view (small enlargement) of an **aerosol** sample collected in an All Glass Impinger (AGI) after 15 minutes of operation. Note the small size of the particles. . .

DRAWING DESC:

DRWD(7)

FIGS. 6A and 6B are graphs of aerodynamic particle size of enviroxime-liposome **aerosol** by TSI particle size instruments.

DRAWING DESC:

DRWD(8)

FIG. 7 is a nomogram derived to estimate **aerosol** dosage based on the concentration of the drug (ribavirin) in aqueous liquid in the **aerosol** generator.

DETDESC:

DETD(2)

As previously set forth, the present invention is directed to small particle aqueous **aerosol** particles containing liposomes and interacted drug liposome combination particles propelled or carried in air or oxygen-enriched air to methods of generating aerosols of them, and to methods of treating patients with them. As the term "Small particle **aerosol**" is used herein, it is defined as a colloid system in which the continuous phase is an air or oxygen-enriched air, and the majority of the **aerosol** particles or droplets is less than 5 microns in diameter with an aerodynamic mass median diameter ranging from 1 to. . . particles and the interacted drug liposome combination particles can readily be converted to a more homogeneous small size by an **aerosol** nebulizer without any loss in effectiveness of the liposomes and interacted drug liposome combination particles while contained in aqueous **aerosol** particles of the above diameter size while propelled or carried in air or oxygen-enriched air. Advantageously, these small particle aqueous **aerosol** droplets containing these liposomes and liposome-drug combinations, when inhaled, provide high concentration on the respiratory epithelium and a steady rate. . . routes of administration. One to several liposomes or liposome-drug particles (<1 micron in diameter) may be contained in a single **aerosol** droplet (1-3 micron, aerodynamic mass median diameter) depending on the concentration of liposome material in the preparation that is to. . . lower respiratory tract in substantial percentages. For example, 1.5 micron particles will deposit 46% of the total inhaled in the **lung** and another 36% in the nose and upper air passages. Such uniform deposition permits treatment of lesions at any level. . .

DETDESC:

DETD(4)

The . . . describes medications of lipophilic nature which may be interacted with the lipid of liposome and be adminstered by small particle **aerosol**.

DETDESC:

DETD(5)
. . .

1

Doses of drugs that interact with liposomes and may be administered in a liposome formulation by small particle **aerosol** inhalation. Average adult doses for some indications are

---

given:

Cardiac glycosides	
Digitoxin	1.2 to 1.6 mg, loading. . . gm/day
Chlorpropamide	100-250 mg/day
Tolbutamide	100-250 mg-3.0 gm/day
Anti-hormone	
Bromocriptine mesylate	1.25-2.5 mg/day
Immune suppressive	
Cyclosporine A	500 mg-1000 mg/day
Anticancer	
Uracil mustard	0.10-0.15 mg/kg weekly for 4 weeks
Methotrexate	
Anti-fungal	
Amphotericin. . .	

DETDESC:

DETD(6)

The . . . but which, if derivatized to be lipophyllic, can be prepared as drugs in Table 1 and be administered as liposome **aerosol**.

DETDESC:

DETD(7)

. . .

water soluble that if suitably derivatized so that they interact with lipid of liposomes can be administered in small particle **aerosol**

Antiasthma	Antiarrhythimic	Tranquilizers
metaproterenol	propanolol	hydroxyzines
aminophylline	atenolol	
theophylline	verapamil	Antihistamines
terbutaline	captopril	pyribenzamine. . .

DETDESC:

DETD(12)

Any . . . active compounds or medications can be interacted with liposomes and that such liposomes are applicable to delivery by small particle **aerosol**.

DETDESC:

DETD(18)

For . . . less than 1 micron up to 10 microns in diameter. The

preparation was then placed in a small particle aqueous **aerosol** generator that used a Collison nebulizer propelled by air or oxygen-enriched air for formation of the small aqueous particles. During. . . were less than 1 micron in diameter and many less than 0.1 microns in diameter. The size of the aqueous **aerosol** particles containing enviroxime-liposomes delivered to the patient is controlled by the operational characteristics of the **aerosol** generator. The majority of these **aerosol** droplets were less than 5 microns in diameter with an aerodynamic mass median diameter ranging from about 1 to 3 microns. Any type of **aerosol** nebulizer can be used which so reduces the size of the liposomes and produces an aqueous **aerosol** in which the continuous phase is air or oxygen-enriched air, a number of which are available on the market. For. . .

DETDESC:

DETD(19)

FIG. . . . in size, ranging from 0.7 microns down to less than 0.03 microns in diameter. Following processing by the small particle **aerosol** generator (SPAG), the liposomes become more homogeneous in size, as shown in FIGS. 3 and 4, with larger ones being. . . that they retain their liposomes characteristics and are multi-lamellar liposomes of "classical" structure after generation in a small particle aqueous **aerosol**.

DETDESC:

DETD(21)

Enviroxime . . . of enviroxime (1-8 mg/mL) and phosphatidylcholine (15 mg/mL) in particles small enough to be administered as a small particle aqueous **aerosol**. By this methodology, doses of 6 to 12 mg/hr can be given to the respiratory tract.

DETDESC:

DETD(32)

A further example of liposome **aerosol** treatment is the administration of **cyclosporine** A combined in liposomes of phosphatidylcholine or of phosphatidylcholine-cholesterol mixtures which are made by Method I.

DETDESC:

DETD(33)

For liposomes of **cyclosporine** A and phosphatidylcholine, phosphatidylcholine (450 mg) in 22.5 mL of chloroform was added to a 500 mL round bottom flask. . . mechanically resuspended by shaking in 30 mL of sterile phosphate buffered saline. Formation of liposomes was confirmed for ratios of **cyclosporine** A to phosphatidylcholine of 1:48 up to 1:12 by specific entrapment of markers. In other experiments, it was established using radiolabeled **cyclosporine** A that more than 83% of the drug was incorporated into the liposomes under these conditions.

DETDESC:

DETD(34)

Liposomes were also prepared by this procedure containing cholesterol in addition to **cyclosporine** A and phosphatidylcholine (Table 4).

Addition of cholesterol increased the quantities of **cyclosporine** A that could be incorporated into liposomes by two-fold. The ratios of **cyclosporine** A to phosphatidylcholine found to form liposomes were 1:48 up to 1:7. Cholesterol was present at one-half the phosphatidylcholine concentration. Again, incorporation of **cyclosporine** A into liposomes confirmed over the range of drug concentrations and formation of liposomal permeability barriers was documented by marker. . .

DETDESC:

DETD(35)

TABLE 4

Characterization of liposomes containing **cyclosporine** A

Chol (mg)	EYPC (mg)	CsA (mg)	Molar Ratio CsA:EYPC	Volume Entrapped	Percent (%) Associated
	7.5. . .		1:7	2.1	82.8
3.75	7.5	3.75	1:4	1.3	76.1

Abbreviations:
Chol, cholesterol; EYPC, egg yolk phosphatidylcholine; CsA, **cyclosporine** A.

DETDESC:

DETD(36)

Liposomes containing 2-4 mg of **cyclosporine** A prepared by the above procedures were also placed in a Collison small particle **aerosol** generator and delivery of drug containing liposomes was confirmed in particles ranging from less than 1 micron to greater than 5 microns. The aerodynamic mass median diameter of the aqueous particles in the **aerosol** was found to be 1.8 to 2.0 microns. This particle size range is similar as observed with other liposome preparations. . .

DETDESC:

DETD(70)

Further . . . 14 are shown in Table 5 in which the preferred methodology for preparation in liposomes, concentration of drug in the **aerosol** reservoir and the amount of drug deliverd in an aqueous erosol by air or oxygen-enriched air in a specified period. . .

DETDESC:

DETD(71)

TABLE 5

Suggested Delivered Dose of Representative Liposome Containing Compounds as Contained in Small Particle Aqueous **Aerosol** Delivered by Air or Oxygen Enriched Air

	Concentration	Duration	Estimated

Example in Reservoir of Delivered Dose.sup.2. . . of compounds to the surface of the lipid bilayer.
.sup.2 Estimated dose based on a 70% efficiency of **aerosol** deposition and a 10 L minute volume for a 70 kg adult, and on currently given dosages.

DETDESC:

DETD(73)

Estimation of dosage of liposome-interacted drugs administered in small particle **aerosol**

DETDESC:

DETD(74)

The dosage of liposome drug preparations in small particle **aerosol** administered by inhalation can be controlled at three different points. The first is the concentration of drug in the liposome.. . .

DETDESC:

DETD(75)

A . . . be achieved is the concentration of liposome-drug preparation that is added to the aqueous vehicle in the reservoir of the **aerosol** generator. This may range from 10 to 40 mg/mL of liposome-drug preparation in the liquid reservoir of the **aerosol** generator.

DETDESC:

DETD(76)

A . . . achieved. Thus, a general formulation can be derived: Total drug administered.apprxeq.Concentration of the drug in the liposome.times.Concentration of liposome in **aerosol** generator.times.Duration of treatment.

DETDESC:

DETD(77)

Retention by patients of drugs following inhalation in small particle **aerosol** can be estimated. The basis for estimates includes particle size distribution, density of particles, concentration of drug in particles, age,. . . factors (Knight, V., Yu, C. P., Gilbert, B. E. , and Divine, G. W. 1988, Estimating the dosage of Ribavirin **Aerosol** According to Age and Other Variables. Journal Infect. Dis. 158(2):443-448). Liposome-drug aerosols suspended in watery media are aqueous aerosols and. . . closely with aqueous aerosols. This is demonstrated in FIGS. 6A and 6B where the particle size distribution of a liposome-enviroxime **aerosol** was measured from a Collison generator (SPAG-2-6000 model). The liposome-enviroxime preparation consisted of 450 mg of egg yolk lecithin and. . . particle size analyzer (TSI, Inc.) was used to count particles. The sample time was 20 seconds and assumed density of **aerosol** particles was 1.0 g/cm.sup.3. The nebulizer pressure was 26 psi and the flow rate was 7.5 lpm. The drying air. . .

DETDESC:

DETD(78)

FIG. 7 shows a nomogram which was derived to estimate **aerosol** dosage based on the concentration of the drug ribavirin in the aqueous liquid of the **aerosol** generator. By determining the ratio of the concentration of ribavirin and enviroxime in the **aerosol** reservoir, the estimated dosage of enviroxime administered in liposomes can be obtained. The ribavirin **aerosol** contains 20 mg/mL of ribavirin in the liquid reservoir at the beginning of treatment and the enviroxime concentration is 4 mg/mL. Thus, to predict the dose of enviroxime **aerosol** retained by the patient, the concentration of enviroxime in the reservoir liquid (4 mg/mL) is divided by the concentration of ribavirin in the reservoir liquid (20 mg/mL). The dose of enviroxime retained after inhalation of **aerosol** would be 20 percent of that of ribavirin retention. Thus, from FIG. 7, a dose of enviroxime for a 25. . . With this methodology, it is possible to estimate the dosage of any drug contained in liposomes administered by small particle **aerosol**. Table 1 shows a list of drugs which are lipophilic in nature and may be prepared in liposomes and administered in small particle **aerosol**. The usual dosages of those drugs by other routes is indicated. In general, dosage by liposome **aerosol** would be appreciably less than that recommended by other routes.

DETDESC:

DETD(79)

Advantageously, small particle aqueous **aerosol** droplets containing interacted liposome-drug combination particles treatment leads to deposition of drug and liposomes throughout the respiratory tract in substantial. . . bacteria or fungi, the diseases will be contained in inflammatory exudates and alveoli and in other anatomical spaces in the **lung** and within tissues of the **lung** at various locations. Aerosolized interacted liposome-drug will be deposited on these sites.

DETDESC:

DETD(80)

In the case of **lung** tumors of primary or secondary origin, the tumor masses would be the site of deposition of **aerosol** interacted liposome-anti cancer drugs.

DETDESC:

DETD(82)

In the case of psychiatrically useful drugs, hormones, or cardioactive agents, systemic absorption following aqueous **aerosol** interacted liposome-drug administration would occur at an even rate without high peaks in plasma concentration thus avoiding potential toxicity and. . .

DETDESC:

DETD(83)

Aqueous **aerosol** droplets containing liposomes alone may replace natural surfactants in the **lung** of victims of drowning, chemical inhalational poisoning, and in premature infants deficient in surfactant.

DETDESC:

DETD(84)

Influenza or other vaccines can be given conveniently in small particle aqueous **aerosol** liposomes deposited by air or oxygen-enriched air directly on immunoreactive cells in the **lung** to elicit locally protecting immune responses. Humoral antibody may also be so stimulated.

DETDESC:

DETD(87)

Thus, while specific examples of a variety of small particle aqueous **aerosol** droplets containing liposome particles and interacted liposome-drug combination particles have been given for purposes of disclosure, the present invention is. . . all drugs or medications and combinations of them interacted with liposomes which can be incorporated in such small particle aqueous **aerosol** droplets for a wide variety of disease. Also, as previously mentioned, the dosage of these liposome-drug combinations vary widely depending. . .

CLAIMS:

CLMS(1)

What is claimed is:

1. Aqueous **aerosol** droplets containing one or more liposome particles, the majority of the mass of the **aerosol** droplets having a diameter from 1 to 5 microns, and having an aerodynamic mass median diameter ranging from about 1. . .

CLAIMS:

CLMS(2)

2. Aqueous **aerosol** droplets containing one or more liposome particles and one or more lipophilic medications interacted with the liposome's membrane, the majority of the mass of the **aerosol** droplets having a diameter from 1 to 5 microns, and having an aerodynamic mass median diameter ranging from about 1. . .

CLAIMS:

CLMS(3)

3. Aqueous **aerosol** droplets containing one or more liposome particles having multiple aqueous compartments and one or more lipophilic medications interacted with membranes of the liposome particles, the majority of the mass of the **aerosol** droplets having a diameter of from 1 to 5 microns, and having an aerodynamic mass median diameter ranging from about. . .

CLAIMS:

CLMS(4)

4. The aqueous **aerosol** droplets of claim 2 wherein, the medication is selected from a lipophilic or a compound made lipophilic by derivatization of. . .

CLAIMS:

CLMS(5)

5. The aqueous **aerosol** droplets of claim 3 where, the one or more medications are selected for man insoluble or a compound made lipophilic. . .

CLAIMS:

CLMS(6)

6. A method of treating a patient comprising, introducing into the respiratory tract of the patient the aqueous **aerosol** droplets of claim 1 by one of air and oxygen enriched air.

CLAIMS:

CLMS(7)

7. A method of treating a ptient comprising, introducing into the respiratory tract of the patient the aqueous **aerosol** droplets of claim 2 by one of air and oxygen enriched air.

CLAIMS:

CLMS(8)

8. A method of treating a patient comprising, introducing into the respiratory tract of the patient the aqueous **aerosol** droplets of claim 3 by one of air and oxygen enriched air.

CLAIMS:

CLMS(9)

9. A method of treating a patient comprising, introducing into the respiratory tract of the patient the aqueous **aerosol** droplets of claim 4 by one of air and oxygen enriched air.

CLAIMS:

CLMS(10)

10. A method of treating a patient comprising, introducing into the respiratory tract of the patient the aqueous **aerosol** droplets of claim 5 by one of air and oxygen enriched air.

CLAIMS:

CLMS(11)

11. A method of generating the aqueous **aerosol** droplets of claim 1 comprising, nebulizing heterogeneous particles of liposomes in an aqueous medium with air or oxygen enriched air by a nebulizer effective to produce the aqueous **aerosol** droplets and homogenize the particles of liposomes.

CLAIMS:

CLMS(12)

12. A method of generating the aqueous **aerosol** droplets of claim 2 comprising, nebulizing the particles of liposomes and the one or more medications with the liposome's membrane. . . of heterogeneous size in an aqeuous medium with air or oxygen enriched air in a nebulizer

effective to produce the **aerosol** droplets and to homogenize the particles without loss of the medications and their activity.

CLAIMS:

CLMS(13)

13. A method of generating the aqueous **aerosol** droplets of claim 3 comprising, nebulizing the particles of liposomes and the one or more lipophilic medications interacted with the. . . of heterogeneous size in an aqueous medium with air or oxygen enriched air in a nebulizer effective to produce the **aerosol** droplets and to homogenize the particles of liposomes without loss of medication and its activity.

CLAIMS:

CLMS(14)

14. A method of generating the aqueous **aerosol** droplets of claim 4 comprising, nebulizing the particles of liposomes and the selected medication of heterogeneous size in an aqueous medium with air or oxygen enriched air in a nebulizer effective to produce the **aerosol** droplets and to homogenize the particles of liposomes without loss of the medication and its activity.

CLAIMS:

CLMS(15)

15. A method of generating the aqueous **aerosol** droplets of claim 5 comprising, nebulizing the liposome particles and the selected medication of heterogeneous size in an aqueous medium with air or oxygen enriched air in an nebulizer effective to produce the **aerosol** droplets and to homogenize the liposome particles without loss of the medication and its activity.

CLAIMS:

CLMS(16)

16. An **aerosol** container having a reservoir containing the liposome particles of claim 1 in n aqueous medium, and having **aerosol** generating means including an air or an oxygen enriched air source in fluid communication with the reservoir effective to produce the aqueous **aerosol** droplets.

CLAIMS:

CLMS(17)

17. An **aerosol** container having a reservoir containing the liposomes and medications of claim 2 in an aqueous medium, and having **aerosol** generating means including an air or oxygen enriched air source in fluid communication with the reservoir effective to produce the aqueous **aerosol** droplets.

CLAIMS:

CLMS(18)

18. An **aerosol** container having a reservoir containing the liposomes and medications of claim 3 in an aqueous medium, and having **aerosol** generating means including an air or oxygen enriched air source in fluid

communication with the reservoir effective to produce the aqueous **aerosol** droplets.

CLAIMS:

CLMS(19)

19. An **aerosol** container having a reservoir containing the liposomes and medications of claim 4 in an aqueous medium, and having **aerosol** generating means including an air or oxygen enriched air source in fluid communication with the reservoir effective to produce the aqueous **aerosol** droplets.

CLAIMS:

CLMS(20)

20. An **aerosol** container having a reservoir containing the liposomes and medications of claim 5 in an aqueous medium, and having **aerosol** generating means including an air or oxygen enriched air source in fluid communication with the reservoir effective to produce the aqueous **aerosol** droplets.

CLAIMS:

CLMS(21)

21. A method of producing the **aerosol** droplets of claim 1 comprising, placing heterogeneous particles of the liposomes in an aqueous medium in an **aerosol** reservoir, and aerosolizing the heterogeneous particles of liposomes with air or oxygen enriched air effective to produce the aqueous **aerosol** droplets and to homogenize the heterogeneous particles of liposomes.

CLAIMS:

CLMS(22)

22. A method of producing the **aerosol** droplets of claim 2 comprising, placing heterogeneous particles of the liposomes and medication in an aqueous medium in an **aerosol** reservoir and aerosolizing the heterogeneous particles of liposomes and medication with air or oxygen enriched air effective to produce the aqueous **aerosol** droplets and to homogenize the heterogeneous particles of liposomes.

CLAIMS:

CLMS(23)

23. A method of producing the **aerosol** droplets of claim 3 comprising, placing the particles of medications interacted with membranes of the liposomes of heterogeneous size in an aqueous medium in an **aerosol** reservoir, and aerosolizing them with air or oxygen enriched air effective to produce the **aerosol** droplets and to homogenize the heterogeneous particles.

CLAIMS:

CLMS(24)

24. A method of producing the **aerosol** droplets of claim 4 comprising, placing the particles of medication interacted with membranes of liposomes of heterogeneous size in an aqueous medium in an **aerosol**

reservoir, and aerosolizing them with air or oxygen enriched air effective to produce the **aerosol** droplets and to homogenize the heterogeneous particles.

CLAIMS:

CLMS(25)

25. A method of producing the **aerosol** droplets of claim 5 comprising, placing the particles of one or more medications interacted with membranes of the liposomes of heterogeneous size in an aqueous medium in an **aerosol** reservoir, and aerosolizing them with air or oxygen enriched air effective to produce the **aerosol** droplets and to homogenize the heterogeneous particles.

US PAT NO: 5,681,556 [IMAGE AVAILABLE] L7: 29 of 51

ABSTRACT:
Disclosed . . . extracts of said cultured lymphocytes, MHC antigens, transplantation rejection suppressive fragments and analogs of MHC antigens in an oral or **aerosol** form. Also disclosed herein are pharmaceutical formulations and dosage forms for use in said methods.

SUMMARY:

BSUM(5)

Tissue . . . cytotoxic agents in an effort to suppress the transplant recipient's immune response against the transplanted organ or tissue. For example, **cyclosporine** (cyclosporin A), a cyclic polypeptide consisting of 11 amino acid residues and produced by the fungus species Tolypocladium inflatum Gams,. . . liver, pancreas and heart (i.e., wherein donor and recipient are of the same species of meals) transplants. However, administration of **cyclosporine** is not without drawbacks as the drug can cause kidney and liver toxicity as well as hypertension. Moreover, use of **cyclosporine** can lead to malignancies (such as lymphoma) and lead to opportunistic infection due to the "global" nature of the immunosuppression. . .

SUMMARY:

BSUM(6)

Preliminary results have shown FK-506 (which has a similar mode of action as **cyclosporine**) to be as potent as **cyclosporine** in its immunosuppressive qualities and to have fewer toxic side effects than **cyclosporine**. However, because studies on FK-506 are only in the early stages, it is not available to the general population. Hence,. . .

SUMMARY:

BSUM(7)

Other drugs and/or therapies which are currently administered (either in conjunction with **cyclosporine** or alone) to suppress the rejection of allogeneic grafts or allografts are also non-specific immunosuppressive drugs or therapies. Steroids, such. . .

SUMMARY:

BSUM(11)

The oral and **aerosol** administration of antigens has also been recognized as an effective way to suppress the immune response in meals to these. . .

SUMMARY:

BSUM(14)

Weiner . . . of 08/070,020, in turn a continuation of 07/896,484, in turn a continuation of 07/595,468. Ser. No. 07/595,468 discloses oral and **aerosol** compositions and pharmaceutical formulations containing insulin which are useful for treating mammals suffering from or at risk for autoimmune diseases. . .

SUMMARY:

BSUM(16)

Weiner . . . 08/053,306 (Ser. No. 08/480,188, a continuation of 08/419,502, has been allowed and the issue fee has been paid) discloses the **aerosol** administration of autoantigens, disease-suppressive fragments of said autoantigens and analogs thereof as an effective method for treating T-cell mediated autoimmune. . .

SUMMARY:

BSUM(21)

The present invention proposes the clinical administration to mammalian graft recipients of alloantigens via oral and **aerosol** routes to induce a tolerance to foreign tissue grafts. The invention will be primarily useful in the field of organ. . . Immunol. 121:1480, 1978; J. Exp. Med. 149:1042, 1979), no disclosure or suggestion of introducing these antigens orally or in an **aerosol** form was made therein.

SUMMARY:

BSUM(24)

A . . . the invention is to provide synthetic compositions and pharmaceutical formulations that may be administrated to mammals via the oral or **aerosol** route to suppress the mammalian immune response to the presence of transplanted tissue or organs.

SUMMARY:

BSUM(27)

It . . . tissue and cultured lymphocytes and specific Major Histocompatibility Complex (MHC) antigens can be administered to mammals via the oral or **aerosol** route to suppress the mammalian immune response to surgically transplanted "non-self" organs or tissues. Because the effect is dependent upon. . .

SUMMARY:

BSUM(30)

Additionally, an **aerosol** delivery system can be prepared with essentially the dosages of splenocyte derivatives or MHC antigens as above and a pharmaceutically suitable carrier or diluent. The **aerosol** formulations can also be administered sometime prior to transplant surgery via the **aerosol** route. These and other improvements will be

described in the following descriptions, drawings and appended claims.

DETDESC:

DETD(10)

"**Aerosol**" refers to finely divided solid or liquid particles that may be created using a pressurized system such as a nebulizer.. . .

DETDESC:

DETD(11)

The "**aerosol** route" of administration means delivery of an **aerosol** formulation to a host via the nasal or oral airway.

DETDESC:

DETD(35)

In an alternative embodiment of the present invention the pharmaceutical formulations of the present invention are administered to mammals in **aerosol** form. It is anticipated that smaller quantities of the allogeneic tissue extracts or MHC antigens, disease suppressive fragments or their analogs will be required to achieve suppression of graft rejection when using the **aerosol** form of administration. This has been found to be the case in treating experimental allergic encephalomyelitis (EAE) with myelin basic. . . The quantity of MHC antigens, disease suppressive fragments or the analogs of such meterials which may be administered in an **aerosol** dosage form would be between about 0.01 mg and 10 mg per kg body weight of a mammal per day. The **aerosol** dosage forms of the present invention may be administered to a patient via the **aerosol** route in a single dosage form or multiple dosage forms. The exact amount to be administered will vary depending on. . .

DETDESC:

DETD(36)

When . . . about 10.sup.9 cell equivalents per kg body weight per day may be administered in single or divided doses in an **aerosol** form.

DETDESC:

DETD(37)

The **aerosol** pharmaceutical formulations of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, and. . . type that are well-known in the art. Specific non-limiting examples of the carriers and/or diluents that are useful in the **aerosol** pharmaceutical formulations of the present invention include water, normal saline and physiologically-acceptable buffered saline solutions such as phosphate buffered saline. . .

DETDESC:

DETD(38)

Examples . . . are physiologically balanced salt solutions, phosphate buffered saline and isotonic saline. The salts that may be employed in preparing the **aerosol** dosage forms of the invention include the

pharmaceutically acceptable salts of sodium and potassium.

DETDESC:

DETD(39)

The . . . antigen or disease suppressive fragments or their analogs according to this alternate embodiment of the present invention is in an **aerosol** or inhaled form. The **aerosol** compositions of the present invention can be administered as a dry powder or in an aqueous solution. Preferred **aerosol** pharmaceutical formulations may comprise, for example, a physiologically-acceptable buffered saline solution containing between about 7 mg and about 700 mg. . .

DETDESC:

DETD(40)

Dry **aerosol** in the form of finely divided solid particles of tissue extracts from spleen cells, MHC antigens disease suppressive fragments or. . .

DETDESC:

DETD(41)

The pharmaceutical formulations of the present invention may be administered via the **aerosol** route by means of a nebulizer, as an example those described in U.S. Pat. Nos. 4,624,251 issued Nov. 25, 1986; 3,703,173 issued Nov. 21, 1972; 3,561,444 issued Feb. 9, 1971 and 4,635,627 issued Jan. 13, 1971. The **aerosol** material is inhaled by the subject to be treated.

DETDESC:

DETD(42)

Other systems of **aerosol** delivery, including for example the pressurized metered dose inhaler (MDI) and the dry powder inhaler as disclosed in Newman, S. P. in Aerosols and the **Lung**, Clarke, S. W. and Davia, D. eds. pp. 197-224, Butterworths, London, England, 1984 can be used in conjunction with the. . .

DETDESC:

DETD(43)

Aerosol delivery systems of the type disclosed herein are available from numerous commercial sources including Fisons Corporation (Bedford, Mass.), Schering Corp.. . .

US PAT NO: 5,788,968 [IMAGE AVAILABLE] L7: 21 of 51

ABSTRACT:
Disclosed . . . extracts of said cultured lymphocytes, MHC antigens, transplantation rejection suppressive fragments and analogs of MHC antigens in an oral or **aerosol** form. Also disclosed herein are pharmaceutical formulations and dosage forms for use in said methods.

SUMMARY:

BSUM(5)

Tissue . . . liver, pancreas and heart (i.e., wherein donor and recipient are of the same species of mammals) transplants. However, administration of **cyclosporine** is not without drawbacks as the drug can cause kidney and liver toxicity as well as hypertension. Moreover, use of. . .

SUMMARY:

BSUM(6)

Preliminary results have shown FK-506 (which has a similar mode of action as **cyclosporine**) to be as potent as cyclosporin in its immunosuppressive qualities and to have fewer toxic side effects than cyclosporin. However,. . .

SUMMARY:

BSUM(11)

The oral and **aerosol** administration of antigens has also been recognized as an effective way to suppress the immune response in mammals to these. . .

SUMMARY:

BSUM(14)

Weiner . . . Treating Or Preventing Type 1 Diabetes By Oral Administration Of Insulin, filed Oct. 10, 1990 now abandoned, discloses oral and **aerosol** compositions and pharmaceutical formulations containing insulin which are useful for treating mammals suffering from or at risk for autoimmune diseases. . .

SUMMARY:

BSUM(16)

Weiner et al., U.S. patent appplication Ser. No. 454,806 filed Dec. 20, 1989 now abandoned, discloses the **aerosol** administration of autoantigens, disease-suppressive fragments of said autoantigens and analogs thereof as an effective method for treating T-cell mediated autoimmune. . .

SUMMARY:

BSUM(21)

The present invention proposes the clinical administration to mammalian graft recipients of alloantigens via oral and **aerosol** routes to induce a tolerance to foreign tissue grafts. The invention will be primarily useful in the field of organ. . . Immunol. 121:1480, 1978; J. Exp. Med. 149:1042, 1979), no disclosure or suggestion of introducing these antigens orally or in an **aerosol** form was made therein.

SUMMARY:

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SUMMARY:

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It . . . tissue and cultured lymphocytes and specific Major Histocompatibility Complex (MHC) antigens can be administered to mammals via the oral or **aerosol** route to suppress the mammalian immune response to surgically transplanted "non-self" organs or tissues. Because the effect is dependent upon-MHC. . .

SUMMARY:

BSUM(30)

Additionally, an **aerosol** delivery system can be prepared with essentially the dosages of splenocyte derivatives or MHC antigens as above and a pharmaceutically suitable carrier or diluent. The **aerosol** formulations can also be administered sometime prior to transplant surgery via the **aerosol** route. These and other improvements will be described in the following descriptions, drawings and appended claims.

DETDESC:

DETD(10)

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DETDESC:

DETD(11)

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DETDESC:

DETD(35)

In an alternative embodiment of the present invention the pharmaceutical formulations of the present invention are administered to mammals in **aerosol** form. It is anticipated that smaller quantities of the allogeneic tissue extracts or MHC antigens, disease suppressive fragments or their analogs will be required to achieve suppression of graft rejection when using the **aerosol** form of administration. This has been found to be the case in treating experimental allergic encephalomyelitis (EAE) with myelin basic. . . The quantity of MHC antigens, disease suppressive fragments or the analogs of such materials which may be administered in an **aerosol** dosage form would be between about 0.01 mg and 10 mg per kg body weight of a mammal per day. The **aerosol** dosage forms of the present invention may be administered to a patent via the **aerosol** route in a single dosage form or multiple dosage forms. The exact amount to be administered will vary depending on. . .

DETDESC:

DETD(36)

When . . . about 10.sup.9 cell equivalents per kg body weight per day may be administered in single or divided doses in an **aerosol** form.

DETDESC:

DETD(37)

The **aerosol** pharmaceutical formulations of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, and. . . type that are well-known in the art. Specific non-limiting examples of the carriers and/or diluents that are useful in the **aerosol** pharmaceutical formulations of the present invention include water, normal saline and physiologically-acceptable buffered saline solutions such as phosphate buffered saline. . .

DETDESC:

DETD(38)

Examples . . . are physiologically balanced salt solutions, phosphate buffered saline and isotonic saline. The salts that may be employed in preparing the **aerosol** dosage forms of the invention include the pharmaceutically acceptable salts of sodium and potassium.

DETDESC:

DETD(39)

The . . . antigen or disease suppressive fragments or their analogs according to this alternate embodiment of the present invention is in an **aerosol** or inhaled form. The **aerosol** compositions of the present invention can be administered as a dry powder or in an aqueous solution. Preferred **aerosol** pharmaceutical formulations may comprise, for example, a physiologically-acceptable buffered saline solution containing between about 7 mg and about 700 mg. . .

DETDESC:

DETD(40)

Dry **aerosol** in the form of finely divided solid particles of tissue extracts from spleen cells, MHC antigens disease suppressive fragments or. . .

DETDESC:

DETD(41)

The pharmaceutical formulations of the present invention may be administered via the **aerosol** route by means of a nebulizer, as an example those described in U.S. Pat. Nos. 4,624,251 issued Nov. 25, 1986; 3,703,173 issued Nov. 21, 1972; 3,561,444 issued Feb. 9, 1971 and 4,635,627 issued Jan. 13, 1971. The **aerosol** material is inhaled by the subject to be treated.

DETDESC:

DETD(42)

Other systems of **aerosol** delivery, including for example the pressurized metered dose inhaler (MDI) and the dry powder inhaler as disclosed in Newman, S. P. in Aerosols and the **Lung**, Clarke, S. W. and Davia, D. eds. pp. 197-224, Butterworths, London, England, 1984 can be used in conjunction with the. . .

DETDESC:

DETD(43)

Aerosol delivery systems of the type disclosed herein are available from numerous commercial sources including Fisons Corporation (Bedford, Mass.), Schering Corp.. . .

US PAT NO: 5,837,699 [IMAGE AVAILABLE] L7: 14 of 51

DETDESC:

DETD(5)

Administering . . . efficacy to systemic safety. The local efficacy in asthma of corticosteroids such as mometasone furoate is assessed by measurement of **lung** function and reduction in frequency and severity of symptoms. Systemic safety of such cortisteroids is usually measured by HPA-axis function;. . .

DETDESC:

DETD(15)

The . . . nedocromil sodium (available from Fisons); immunosuppressive agents such as methotrexate sodium (available from Astra Pharmaceutical Products, Inc.), oral gold, or **cyclosporine** A (available from Sandoz under the SANDIMMUNE.RTM. tradename); bronchodilators such as albuterol (available from Schering Corporation under the PROVENTIL.RTM. tradename). . .

DETDESC:

DETD(16)

The . . . aerosolized drugs by use of nebulizers and metered-dose inhalers such as used to deliver VANCENASE.RTM. (brand of beclomethasone dipropionate) inhalation **aerosol** (available from Schering Corporation, Kenilworth, N.J.) is disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Co. Easton, Pa., 15th Ed.. . .

DETDESC:

DETD(21)

For treatment of allergic and/or inflammatory diseases of the lower airways and **lung** parenchyma especially diseases such as asthma, chronic obstructive pulmonary disease ("COPD"), granulomatus diseases of the lungs and lower airway passage,. . .

DETDESC:

DETD(33)

In . . . mcg/day, beclomethasone dipropionate (BDP) 336 mcg/day, or placebo. All treatment regimens consisted of BID dosing for 4 weeks. PROVENTIL inhalation **aerosol** (albuterol, USP) was supplied as rescue medication.

DETDESC:

DETD(87)

Comparison . . . bioavailability was greater following administration

with the Gentlehaler.TM. compared to MDI administration. This may have been the result of enhanced **lung** deposition of drug due to the use of a spacer device in the Gentlehaler.TM. . The Gentlehaler.TM. device is a. . .

US PAT NO: 5,886,026 [IMAGE AVAILABLE] L7: 6 of 51

DRAWING DESC:

DRWD(30)

FIG. 27 is a photograph of a **lung**. Briefly, in addition to large liver tumors, metastasis to the **lung** is common. Such metastases are evident by the presence of small white lobules seen throughout the **lung**.

DETDESC:

DETD(19)

Anti-angiogenic . . . nitrosoureas, DNA alkylating agents. topoisomerase inhibitors, purine antagonists and analogs, pyrimidine antagonists and analogs, alkyl sulfonates); immunosuppressive agents (e.g., adrenocorticosteroids, **cyclosporine**); sense or antisense oligonucleotides (e.g., DNA, RNA, nucleic acid analogues (e.g., peptide nucleic acids) or any combinations of these); and. . .

DETDESC:

DETD(45)

A . . . are most likely to spread to the liver include: cancer of the stomach, colon, and pancreas; melanoma; tumors of the **lung**, oropharynx, and bladder; Hodgkin's and non-Hodgkin's lymphoma; tumors of the breast, ovary, and prostate. Each one of the above-named primary. . .

DETDESC:

DETD(62)

Within . . . the stomach. Cancer of the esophagus or invasion by cancer arising in adjacent organs (e.g., cancer of the stomach or **lung**) results in the inability to swallow food or saliva. Within this embodiment, a preinsertion examination, usually a barium swallow or. . .

DETDESC:

DETD(63)

Within . . . to the lungs. Blockage of the trachea by cancer, invasion by cancer arising in adjacent organs (e.g., cancer of the **lung**), or collapse of the trachea or bronchi due to chondromalacia (weakening of the cartilage rings) results in inability to breathe.. . .

DETDESC:

DETD(70)

Representative . . . Cysts and Colloid Cysts); and Metastatic Tumors (which can be derived from virtually any tumor, the most common being

from **lung**, breast, melanoma, kidney, and gastrointestinal tract tumors).

DETDESC:

DETD(224)

Nanospray . . . suspension of 0.1 .mu.m to 1 .mu.m microparticles may be created suitable for deposition onto tissue through a finger pumped **aerosol**. Equipment and materials which may be utilized to produce nanospray include 200 ml water jacketed beaker (Kimax or Pyrex), Haake. . . 100, 0.1 mg), Mettler digital top loading balance (AE 163, 0.01 mg), automatic pipetter (Gilson), sterile pipette tips, pump action **aerosol** (Pfeiffer pharmaceuticals) 20 ml, laminar flow hood, Polycaprolactone ("PCL"--mol wt 10,000 to 20,000; Polysciences, Warrington, Pa. USA), "washed" (see previous). . .

DETDESC:

DETD(232)

Cap . . . saline. The quantity of saline used is dependent on the final required suspension concentration (usually 10% w/v). Thoroughly rinse the **aerosol** apparatus in sterile saline and add the nanospray suspension to the **aerosol**.

DETDESC:

DETD(402)

Similar . . . established within the lumen of the stent (FIG. 25 and 26). FIG. 27 shows that metastasis had occurred within the **lung**.

=> d his

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     (FILE 'USPAT' ENTERED AT 15:55:03 ON 05 OCT 1999)
L1           707 S CYCLOSPORINE
L2            24 S E LUNG
                 E LUNG
L3         20224 S E3
L4           271 S L1 AND L3
                 E AEROSOL
L5         28701 S E3
L6            98 S L1 AND L5
L7            51 S L4 AND L6
```

=> d l7 51 29 21 14 6

51. 5,049,388, Sep. 17, 1991, Small particle **aerosol** liposome and liposome-drug combinations for medical use; Jack V. Knight, et al., 424/450; 264/4, 4.1; 424/43; 428/402.2 [IMAGE AVAILABLE]

29. 5,681,556, Oct. 28, 1997, Method and compositions for suppressing allograft rejection in mammals; Howard L. Weiner, et al., 424/85.1, 85.2; 514/8; 530/395 [IMAGE AVAILABLE]

21. 5,788,968, Aug. 4, 1998, Methods and compositions for suppressing allograft rejection in mammals; Howard L. Weiner, et al., 424/184.1, 185.1; 530/350 [IMAGE AVAILABLE]

14. 5,837,699, Nov. 17, 1998, Use of mometasone furoate for treating

upper airway passage diseases; Joel A. Sequeira, et al., 514/169, 172, 176, 182 [IMAGE AVAILABLE]

6. 5,886,026, Mar. 23, 1999, Anti-angiogenic compositions and methods of use; William L. Hunter, et al., 514/449 [IMAGE AVAILABLE]

=> s tacolimus

L8 0 TACOLIMUS

=> s tacrolimus

L9 57 TACROLIMUS

=> d his

(FILE 'USPAT' ENTERED AT 15:55:03 ON 05 OCT 1999)

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L1          707 S CYCLOSPORINE
L2           24 S E LUNG
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L6           98 S L1 AND L5
L7           51 S L4 AND L6
L8            0 S TACOLIMUS
L9           57 S TACROLIMUS
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=> s l9 and l5

L10 16 L9 AND L5

=> d l10 1-16

1. 5,952,371, Sep. 14, 1999, Triterpene derivatives with immunosuppressant activity; Robert K. Baker, et al., 514/443; 549/456 [IMAGE AVAILABLE]

2. 5,939,528, Aug. 17, 1999, Crystalline FRAP complex; Jon C. Clardy, et al., 530/350; 536/23.1, 23.5 [IMAGE AVAILABLE]

3. 5,922,729, Jul. 13, 1999, Water soluble polymer-**tacrolimus** conjugated compounds and process for preparing the same; Pan Sup Chang, et al., 514/291; 540/456 [IMAGE AVAILABLE]

4. 5,883,119, Mar. 16, 1999, Triterpene derivatives with immunosuppressant activity; Robert K. Baker, et al., 514/450, 397, 444; 548/311.7; 549/60, 268, 354 [IMAGE AVAILABLE]

5. 5,877,021, Mar. 2, 1999, B7-1 targeted ribozymes; Dan T. Stinchcomb, et al., 435/366, 6, 91.31, 320.1, 325; 536/23.1, 23.2, 24.5 [IMAGE AVAILABLE]

6. 5,874,594, Feb. 23, 1999, Triterpene derivatives with immunosuppressant activity; Robert K. Baker, et al., 549/456, 29, 41, 429 [IMAGE AVAILABLE]

7. 5,874,441, Feb. 23, 1999, Carbocyclic and hetertocyclic fused-ring quinolinecarboxylic acids useful as immunosuppressive agents; Ronald Louis Magolda, et al., 514/285, 287; 546/64, 70 [IMAGE AVAILABLE]

8. 5,840,736, Nov. 24, 1998, Methods and compositions for stimulating neurite growth; Robert E. Zelle, et al., 514/332, 12, 341 [IMAGE AVAILABLE]

9. 5,811,434, Sep. 22, 1998, Methods and compositions for stimulating neurite growth; Robert E. Zelle, et al., 514/307, 237.2, 314, 315, 318, 330, 332, 351; 544/129; 546/139, 192, 193, 194, 245, 256, 300 [IMAGE AVAILABLE]

10. 5,807,743, Sep. 15, 1998, Interleukin-2 receptor gamma-chain ribozymes; Dan T. Stinchcomb, et al., 435/366, 6, 91.31, 320.1, 325; 536/23.1, 23.2, 24.5 [IMAGE AVAILABLE]

11. 5,780,484, Jul. 14, 1998, Methods for stimulating neurite growth with piperidine compounds; Robert E. Zelle, et al., 514/316, 12, 237.2, 314, 317, 318 [IMAGE AVAILABLE]

12. 5,763,478, Jun. 9, 1998, Triterpene derivatives with immunosuppressant activity; Robert K. Baker, et al., 514/450; 549/268 [IMAGE AVAILABLE]

13. 5,747,506, May 5, 1998, Isoquinoline compounds, compositions containing them and their pharmaceutical uses; Reto Naef, 514/307; 546/144 [IMAGE AVAILABLE]

14. 5,696,156, Dec. 9, 1997, Triterpene derivatives with immunosuppressant activity; Robert K. Baker, et al., 514/450; 549/268, 354 [IMAGE AVAILABLE]

15. 5,679,705, Oct. 21, 1997, Triterpene derivatives with immunosuppressant activity; Robert K. Baker, et al., 514/450; 549/268, 354 [IMAGE AVAILABLE]

16. 5,635,161, Jun. 3, 1997, **Aerosol** drug formulations containing vegetable oils; Akwete L. Adjei, et al., 424/45, 46; 514/937 [IMAGE AVAILABLE]

=> d l11 16 kwic

'L11' NOT FOUND

=> d l10 16 kwic

US PAT NO: 5,635,161 [IMAGE AVAILABLE] L10: 16 of 16
TITLE: **Aerosol** drug formulations containing vegetable oils

ABSTRACT:
Pharmaceutical compositions for **aerosol** delivery comprising (a) a medicament, (b) a non-chlorofluorocarbon propellant, and (c) a vegetable oil or a pharmaceutically acceptable derivative thereof,. . .

SUMMARY:

BSUM(2)

The present invention relates to drug formulations for **aerosol** delivery which are compatible with halogenated alkane propellants, and especially to excipients which are useful therein. In particular, the invention. . .

SUMMARY:

BSUM(4)

Pulmonary . . . of peptide and protein biotherapeutics (and also non-peptide drugs) is a rapidly growing area in drug delivery. To this end, **aerosol** preparations of such medicaments have been developed as a means of conveyance to the respiratory system. In order for aerosols. . . be effective, several factors must be considered in their formulation. One factor to consider is the intended application of the **aerosol** drug, i.e. whether the drug is intended for systemic or topical application and/or for sustained or immediate release. For example,. . . diffusion and phagocytosis have been proposed as primary mechanisms for drug absorption. In this situation, it is preferrable that the **aerosol** be formulated to release particles between 1-5 .mu.m in size in order to overcome the lung's formidable barriers to particle. . .

SUMMARY:

BSUM(5)

Aerosols are generally described as dispersions of medicament in a continuous phase. Preparations currently in use include both suspension and solution **aerosol** formulations. Suspension aerosols contain solid particles of a medicament of interest. The particles of the suspension must be pre-milled to. . .

SUMMARY:

BSUM(7)

Unfortunately, . . . or crystallization, for example) of the medicinally active compound in the reservoir of the inhaler, to facilitate uniform dosing upon **aerosol** administration, and to provide an **aerosol** spray discharge having a favorable respirable fraction (that is, a particle size distribution such that a large portion of the. . .

SUMMARY:

BSUM(9)

Surprisingly, . . . for the valve used in an MDI product without the need for additional lubricants, thus aiding reliable functioning of the **aerosol** device throughout the life of the product. It has also been found that oils can be formulated to produce a. . .

SUMMARY:

BSUM(10)

Significant . . . good lung deposition efficiencies and respirable fractions comparable to those obtained with known CFC-propellant formulations. It is thus expected that **aerosol** formulations comprising such oils will be useful for the delivery of both peptide and non-peptide pharmaceutical medicaments for which MDI. . .

SUMMARY:

BSUM(12)

According to one aspect of the present invention, pharmaceutical compositions are disclosed which are useful for **aerosol** delivery, as

for example by inhalation and pulmonary absorption, comprising a therapeutically effective amount of a medicament, a halogenated alkane. . .

SUMMARY:

BSUM(13)

The . . . drugs. Preferred drugs are LHRH analogs, 5-lipoxygenase inhibitors, immunosuppressants (such as cyclosporin A, cyclosporin B, cyclosporin G, rapamycin, ascomycin and **tacrolimus**), antiallergens, anticholinergics and mucolytics (such as ipratropium, cromolyn and DNase), and steroids (such as flunisolide and dexamethasone) and bronchodilators. Especially. . .

DETDESC:

DETD(2)

It is expected that both ozone depleting and non-ozone depleting **aerosol** propellants may be used with the compositions and methods of the present invention. These include for example, the traditionally used. . .

DETDESC:

DETD(17)

The . . . such as leuprolide acetate, the intended daily dose may range from about 0.01 to about 5 mg/day; accordingly, where an **aerosol** inhaler is to be used several times a day with a discharge volume of between about 5 and about 250. . .

DETDESC:

DETD(18)

The . . . medicament which has been milled or otherwise reduced to a desired particle size, and placing the mixture in a suitable **aerosol** container or vial. After sealing the container, an **aerosol** propellant is introduced and the system is agitated to fully blend the ingredients. Alternatively, the vegetable oil and medicament may. . . as for example under temperature and pressure conditions which permit the medicament to be milled while mixed with a liquid-phase **aerosol** propellant. It is expected that, for any particular combination of medicament, propellant and vegetable oil, the ideal order of addition. . .

DETDESC:

DETD(26)

MDI . . . manner: For each test formulation, about 5 mL (or 7.4 grams) of glass beads were placed into a suitable glass **aerosol** container (vial), along with 100 mg to 250 mg drug and a vegetable oil in the amounts needed to produce. . .

DETDESC:

DETD(30)

A . . . leuprolide acetate (Table 2a) or (2) 5-LO inhibitor #1 (Table 2b) in the amounts indicated and placed in appropriate transparent

aerosol containers (vials). (Leuprolide acetate and its preparation are described in U.S. Pat. No. 4,005,063, issued Jan. 25, 1977, which is. . .

CLAIMS:

CLMS(1)

What is claimed is:

1. A pharmaceutical composition for **aerosol** delivery comprising a medicament suitable for pulmonary delivery, a halogenated alkane propellant and a biocompatible C.sub.16+ unsaturated vegetable oil having. . .

CLAIMS:

CLMS(7)

7. . . . to claim 5 wherein the peptide is an immunosuppressant selected from cyclosporin A, cyclosporin B, cyclosporin G, rapamycin, ascomycin and **tacrolimus**.

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1. 5,952,371, Sep. 14, 1999, Triterpene derivatives with immunosuppressant activity; Robert K. Baker, et al., 514/443; 549/456 [IMAGE AVAILABLE]

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